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provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of

(1) SEQ ID NO:4, 5, 6, 7, 8, or 9,

(2) complements of (1), and

(3) fragments of (1) and (2).

REMARKS

Claims

Claims 1-7, 9, 11, and 50, are pending in the application.

Claim 1 is amended to eliminate the "comprising" language in the preamble to better clarify the subject matter of the claim sought.

Claim 1 is further amended for clarity to refer to "a nucleic acid molecule which hybridizes" instead of "nucleic acid molecules which hybridize" in clause (a).

Claim 1 is further amended for clarity to recite "the nucleic acid of SEQ ID NO:1" instead of "a nucleic acid of SEQ ID NO:1" in line 3 of claim 1.

Claim 1 is further amended to recite "polypeptide that binds a tyrosine kinase and regulates its expression" instead of "cbl-SL polypeptide." Support for this amendment can be found throughout the application and at least on page 8, line 27 - page 9, line 14, and the Examples).

Claim 1 is further amended to eliminate the subject matter in clause (b) of claim 1 as originally filed, relating to "deletions, additions and substitutions of a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1 which codes for a cbl-SL polypeptide, and which code for a respective cbl-SL polypeptide."

Claim 4 is further amended for clarity to eliminate reference to GenBank Accession numbers. The sequences excluded from the subject matter of claim 4 are now identified using their SEQ ID NO. Support for this amendment can be found throughout the application and at least on page 8 under the Brief Description of the Sequences and the Sequence Listing.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 1-7, 9, 11, and 50 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such as way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

According to the Examiner, "the specification discloses no evidence (i.e., working examples) of any association between aberrant expression of cbl-SL and any cancer," and "thus, said diagnosis or treatment would be highly unpredictable and require undue experimentation."

It is the Applicants' understanding that the Examiner questions the "enablement of use" of the claimed subject matter (i.e., cbL-SL nucleic acids that encode cbl-SL polypeptides, and compositions thereof). According to the specification:

> "Cbl-SL according to the invention is an isolated nucleic acid molecule that comprises a nucleic acid molecule of SEQ ID NO:1, and codes for a ~50kd protein that is believed to play a role in the regulation of a cell's growth, differentiation and proliferation. The sequence of the human cbl-SL cDNA is presented as SEQ ID NO:1, and the predicted amino acid sequence of this cDNA's encoded protein product is presented as SEQ ID NO:2. Cbl-SL associated functions are believed to be mediated by cbl-SL's binding to other molecules and polypeptides. "Cbl-SL activity," as used herein, refers to the specific binding of cbl-SL to a tyrosine kinase. ...[sic]. ...More preferably, Cbl-SL binds phosphorylated tyrosine kinases and decreases the level of phosphorylation of the tyrosine kinase, and/or dowregulates (or inhibits) expression of the tyrosine kinase. (Detailed Description of the Invention, page 8, line 27 - page 9, line 14, and the Examples).

Thus, Applicants teach that a cbl-SL polypeptide binds a tyrosine kinase and regulates its expression. Tyrosine kinases are well known in the art as 'key' molecules, controlling pathways that regulate a cell's growth, differentiation and proliferation. Tyrosine kinases have been implicated in the genesis of different forms of cancer. For example, the epidermal growth factor receptor (EGFR) subfamily of tyrosine kinases has been implicated in the development and progression of the majority of the most common human epithelial cancers, including breast cancer. In the past 15 years, different approaches have been developed to block EGFR activation and/or function in cancer cells. Several abstracts and a representative article on the association of EGFR and cancer appear in Appendix A,[1] enclosed herein. Further information on EGFR and its function can be obtained through the Internet (e.g., http://www.osip.com/programs/cancer/egfr_tutorial/#). General information on tyrosine kinases can be obtained through several textbooks, including "Molecular Biology of the Cell, Alberts, B., et al., Garland Publishing, Inc., 1994, New York," (and/or through the Internet and NCBI at http://www.ncbi.nlm.nih.gov/books/mboc/mboc.cgi?code=150303480625145).

[1] Noonberg SB, and Benz CC, *Drugs*, 2000 Apr;59(4):753-67 (Abstract); Raymond E, et al., *Drugs*, 2000, 60 Suppl 1:15-23; discussion 41-2 (Abstract); Ciardiello F, *Drugs*, 2000, 60 Suppl 1:25-32; discussion 41-2 (Abstract); Hortobagyi GN, *Cancer*, 2000, Jun 15;88(12 Suppl):3073-9 (Abstract); Huang SM and Harari PM, *Invest New Drugs*, 1999, 17(3):259-69 (Abstract); and Pollack VA, et al., *J Pharmacol Exp Ther*, 1999, Nov;291(2):739-48.

Throughout the specification Applicants teach that a cbl-SL polypeptide binds a tyrosine kinase and regulates its expression. A specific example of such function is described in detail in the specification under Example 6. Applicants show in Example 6 (including Figure 8) that a cbl-SL polypeptide facilitates the downregulation of EGFR. Such function is highly desirable in the treatment of cancer as established in the art (exemplified by the articles appearing in Appendix A).

The Examiner further states that "the specification further fails to provide sufficient evidence to establish that any cbl-SL protein is even actually expressed."

Respectfully, Applicants disagree. Applicants teach that (i) a cbl-SL mRNA is expressed in specific tissues and cell lines (see at least Figures 1 and 2, and Example 2 on page 44), and (ii) a native cbl-SL polypeptide of ~ 50kd is recognized by a cbl-SL specific antisera (raised against an immunogenic peptide sequence encoded by a nucleic acid of Claim 1) (see at least Figures 4A and 4B, and Example 3). The exact size for a cbl-SL polypeptide on a denaturing SDS-PAGE gel is of secondary importance in the experiments described in Example 3 of the specification; Applicants were able to show that a native (endogenous) cbl-SL polypeptide exists, and it is different from the cbl and cbl-b polypeptides of the prior art.

According to the Examiner, "no *in vivo* biological activity is established for the naturally expressed protein (should it exist) or any of the claimed variants or fragments thereof."

Respectfully, Applicants disagree. As argued above, Applicants teach at least one specific cbl-SL function (regulation of tyrosine kinase expression) and cbl-SL utility (cancer treatment).

Claim 1 as amended herewith explicitly refers to, *inter alia*, nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1, and which code for a polypeptide that binds a tyrosine kinase and regulates its expression.

With regard to variants and fragments, the Examiner states that "the recitation in claim 1 of nucleic acids encoding polypeptides comprising 'deletions, additions and substitutions', as well as nucleic acids 'which hybridize under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1,' opens the claim to include nucleic acid molecules that encode a virtually unlimited number of polypeptides," and that "there is insufficient written description to show that Applicant was in possession of any cbl-SL nucleic acids including those with deletions, substitutions, additions; or fragments, unique fragments, or compliments; [etc., *sic*]."

Respectfully, Applicants disagree. It is a specific limitation of the claim that the nucleic acid molecules of claim 1 also code for a cbl-SL polypeptide (or, *hereinafter* the present amendment, "a polypeptide that binds a tyrosine kinase and regulates its expression"). Therefore, the nucleic acid molecules of claim 1 encode a definite number of polypeptides with a specific function.

However, in order to expedite prosecution, Applicants have eliminated clause (b) of Claim 1 as originally filed directed to "deletions, additions and substitutions of a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1 and which codes for a cbl-SL polypeptide, and which code for a respective cbl-SL polypeptide" thus rendering the rejection of Claim 1 under 35 U.S.C. §112, first paragraph, with respect to the 'deletions, additions and substitutions' clause, moot.

With regard to the "hybridization" language of claim 1, Applicants respectfully direct Examiner's attention to the U.S.P.T.O.'s published "Synopsis of Application of Written Description Guidelines" (www.uspto.gov/web/menu/written.pdf), and in particular to Example 9, entitled "Hybridization," pp.35-37.

The hypothetical claim in Example 9 of the guidelines reads as follows:

> "An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity."

The analysis section following the hypothetical claim reads as follows:

> "A review of the full content of the specification indicates that the *essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO: 1 under highly stringent conditions and encodes a protein with a specific function.* The art indicates that hybridization techniques using a known DNA as a probe under highly stringent conditions were conventional in the art at the time of filing.
>
> *The claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity.*
>
> The search of the prior art indicates that SEQ ID NO: 1 is novel and unobvious.
>
> There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus.
>
> There is actual reduction to practice of the disclosed species.
>
> Now turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs.
>
> *Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the*

level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

The Example concludes that *"[t]he claimed invention is adequately described."*

In an analysis similar to the one provided in Example 9 of the guidelines, the specification of the present invention teaches that the essential feature of the claimed invention is the isolated nucleic acid that hybridizes to SEQ ID NO:1 under stringent conditions and encodes a protein (cbl-SL) with a specific function (*cbl-SL activity:* binding of a tyrosine kinase and regulating the tyrosine kinase's expression).

The term "stringent conditions" is analogous to the term "highly stringent conditions" utilized in Example 9 of the guidelines. Example 9 defines "highly stringent conditions" as "6 x SSC and 65°C". Applicants' specification (see page 11, lines 4 - 24) refers to an example of "stringent conditions," as:

> "... hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid.

Stringent conditions used in the hybridization of nucleic acids are well in the art and may be found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. (See also Applicants arguments under the 35 U.S.C. §112, second paragraph, rejections).

Thus, the art indicates that hybridization techniques using a known DNA as a probe under stringent conditions were conventional in the art at the time of filing.

Claim 1 of the present invention is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity (i.e., binding of a tyrosine kinase and regulating the tyrosine kinase's expression).

The search of the prior art indicates that SEQ ID NO: 1 is novel and non-obvious.

There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus.

There is actual reduction to practice of the disclosed species.

A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the stringent hybridization conditions set forth in the claim yield structurally similar DNAs.

Thus, a representative number of species is disclosed, since stringent hybridization conditions (as described in the specification) in combination with the coding function of DNA (i.e., induction of protein synthesis in an epithelial cell) and the level of skill and knowledge in the art are adequate to determine that Applicants were in possession of the claimed invention. Therefore, Applicants' claimed invention is adequately described.

In view of the foregoing amendments and arguments Applicants respectfully request that the foregoing rejections of claims under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claims Under 35 U.S.C. §112 (second paragraph)

Claims 1-7, 9, 11, and 50, stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

According to the Examiner, "a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of the nucleic acid of SEQ ID NO:1 is indefinite because the hybridizations conditions have not been defined."

Respectfully, Applicants disagree. The arguments presented above with respect to the meaning of "stringent conditions" are reiterated here. The term "stringent conditions" is a term commonly used in the art. With nucleic acids, hybridization conditions are said to be stringent typically under conditions of low ionic strength and a temperature just below the melting temperature (T_m) of the DNA hybrid (typically, about 3°C below the T_m of the hybrid). Higher stringency makes for a more specific correlation between the probe sequence and the target.

Stringent conditions used in the hybridization of nucleic acids are well known in the art and may be found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York.

An example of "stringent conditions" is given in the specification as "...hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, 2mM EDTA)." The conditions given in Example 9 of the "Synopsis of Application of Written Description Guidelines," i.e., 6 x SSC and 65°C, are also stringent conditions. In a further example, an alternative to the use of an aqueous hybridization solution is the use of a formamide hybridization solution. Stringent hybridization conditions can thus be achieved using, for example, a 50% formamide solution and 42°C. One of ordinary skill in the art will be able to manipulate the conditions in a manner to permit, for example, the clear identification of homologs and alleles of cbl-SL nucleic acids of the invention.

Applicants believe that the term "stringent conditions" is well defined in the art, typically determined by the melting temperature (T_m) of the hybrid DNA complex.

In view of the foregoing arguments, Applicants respectfully request that the foregoing rejections of claims under 35 U.S.C. §112, second paragraph, be withdrawn.

SUMMARY

Applicants believe that each of the pending claims is in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (Extension 343).

Respectfully Submitted,

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Attorney's Docket No.: **B0801/7159 (ERP/KA)**
Date: April 2, 2001
x04/02/01

MARKED-UP CLAIMS

1 (Amended). An isolated nucleic acid molecule [, comprising] selected from the group consisting of:

(a) a nucleic acid molecule[s] which hybridizes under stringent conditions to a molecule consisting of [a] the nucleic acid of SEQ ID NO:1 and which codes for a [cbl-SL polypeptide] polypeptide that binds a tyrosine kinase and regulates its expression,

[(b) deletions, additions and substitutions of (a) which code for a respective cbl-SL polypeptide,]

(b[c]) nucleic acid molecules that differ from the nucleic acid molecules of (a) [or (b)] in codon sequence due to the degeneracy of the genetic code, and

(c[d]) complements of (a), [(b)] or (b[c]).

4. (Amended) An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of nucleic acid molecule of SEQ ID NO:1,

(b) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of

(1) SEQ ID NO:4, 5, 6, 7, 8, or 9 [sequences having the database accession numbers of Table I],

(2) complements of (1), and

(3) fragments of (1) and (2).